Division of Establishment Licensing
Office of Establishment Licensing and Product Surveillance
Center for Biologics Evaluation and Research
Food and Drug Administration

MEMORANDUM

DATE: May 9, 1997

TO: File Ref No. 97-0260

FROM: Deborah Trout DT
Regulatory Reviewer, OELPS/DEL/HFM-206

SUBJECT: Review of IDEC Pharmaceuticals Corp.
BLA

I have completed my review of IDEC Pharmaceuticals Corp., BLA. A summary of my comments follows with suggestion of things which should be covered during the inspection.

HVAC

The environmental monitoring has not been properly defined in the submission. What are the alert and action limits for viables and nonviables in the manufacturing area? What is the routine frequency of sampling for all classified areas?

Inspection issues:

- The environmental monitoring SOPs should be reviewed on inspection.
- Review environmental data collected during validation.

Water System

Inspection issues:

- Review the SOPs for routine water monitoring, and sampling parameters for the WFI system as well as validation data.

Raw Material

Inspection issues:

- Volume 5, page 25. Is the [redacted] used for transporting raw materials between the warehouse and the manufacturing facility, temperature controlled? Has this procedure been validated?

(b)(4)

Buffer Preparation

Inspection issues:

- Volume 6, page 166, states that buffer tanks are cleaned using the portable, programmable and validated CIP system method that consists of hot caustic and hot acid washes, water rinses, and final HWFI rinse followed by an air purge. The submission also states the tanks may also be cleaned manually using a water rinse, followed by an HWFI rinse. What parameters are applied to determine which procedure is appropriate?

Cell Culture

Inspection issues:

- Volume 3, page 48 states that gentamicin will be added to cell culture as a final prophylactic measure to prevent mycoplasma contamination, please provide rational for antibiotic selection, and concentration.

Bioreactors

Inspection issues:

- Review the protocol and the data generated for the tank integrity validation, i.e., prevention of contamination of the tank due to poor gasket seating, misaligned values or flanges, loose connections etcetera.

- Verify and review bioreactor SOPs not included in the submission

    a. Equipment preparation
    b. Vessel steam sterilization
    c. Medium addition
    d. Inoculation
    e. Aseptic sampling
    f. Transfer to subsequent reactor
    g. Equipment cleaning

Transfer Lines

Inspection issues:

- Please review validation protocols for all transfer lines sterilized via SIP.

Equipment

Inspection issues:

- Following sterilization of equipment is there a time limit after which equipment must be resterilized? Have these time limits been validated?

- Have time limits been set for how long the product can sit on the equipment before it's cleaned? Have these limits been validated?

General

Inspection issues:

(b)(4)

- The submission states that [—] µm filters are used in several sterilizing steps, are these filters to be used multiple times? In the cases where these filters are used multiple times, how are they cleaned and stored between uses, and has the process been validated?

Computer Controlled Process

Inspection issues:

The computer controlled processes have not been properly defined in the submission. Some general questions that should be asked when it's determine which critical process are computer controlled:

- How are computer controlled processes handled in the event of computer shutdowns (e.g., power failure). What is the disposition of the computer's memory content (program and data) upon computer shutdown?

- Are shutdown recovery procedures in place? Where is the point of restart in the cycle (e.g., At the initial step, a random step or the point of shutdown)?

- Does the system have the ability to run manually in the event of computer shutdown? How are manual procedures documented in the event of computer shutdown?

- 21 CFR 211.68(a) states that computers may be used in the manufacture of drug products. If such equipment is used it shall be routinely calibrated and inspected to assure proper performance. What type of calibration and inspection program

do you have in place for this computer system? Have they been validated?

- What functions are linked to alarms? What are the alarm thresholds for critical process conditions and can these threshold be changed by the operator? Are alarm activations documented?